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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/756,690	01/09/2001	Orville G. Kolterman	030639.0066.UTL	4666
44638	7590	10/29/2007		
Intellectual Property Department Amylin Pharmaceuticals, Inc. 9360 Towne Centre Drive San Diego, CA 92121			EXAMINER JIANG, DONG	
			ART UNIT	PAPER NUMBER
			1646	
			MAIL DATE	DELIVERY MODE
			10/29/2007	PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

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**GROUP 1600**

**BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES**

Application Number: 09/756,690  
Filing Date: January 09, 2001  
Appellant(s): KOLTERMAN ET AL.

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Suet M. Chong  
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed 6/13/07 appealing from the Office action mailed 12/14/06.

**(1) Real Party in Interest**

A statement identifying by name the real party in interest is contained in the brief.

**(2) Related Appeals and Interferences**

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

**(3) Status of Claims**

The statement of the status of claims contained in the brief is correct.

**(4) Status of Amendments After Final**

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

**(5) Summary of Claimed Subject Matter**

The summary of claimed subject matter contained in the brief is correct.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

**(7) Claims Appendix**

The copy of the appealed claims contained in the Appendix to the brief is correct.

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**(8) Evidence Relied Upon**

Beeley et al., WO 98/30231, 7-1998.

Karpe et al. Differences in postprandial concentration of VLDL and chylomicron remnants between normotriglyceridemic and hypertriglyceridemic men with and without coronary heart disease. *Metabolism*, 1999, 48:301-307.

US6,326,396, WAGLE et al., 7-2001.

Beers et al., the Merck Manual, 17<sup>th</sup> edition, 1999, pages 200-203.

Beers et al., the Merck Manual, 17th edition, 1999, page 2550.

**(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims:

***Claim Rejections - 35 USC § 103(a)***

Claims 1-14, 24-36 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Karpe et al. (*Metabolism*, 1999, 48:301-307) and Beeley et al. (WO 98/30231, 7/16/98).

Karpe discloses that the postprandial elevation of plasma triglycerides is more closely linked to the risk of developing coronary heart disease (CHD) than the fasting level, and that the plasma triglyceride concentration measured 6 hours after a mixed meal was associated with signs of early atherosclerosis in healthy men (page 301, the second paragraph of the left column; and page 306, the last paragraph of the right column). Note, the term "postprandial" merely means after a meal. Karpe does not teach a method for lowering triglyceride levels with an exendin.

Beeley teaches a method of treatment by administering an exendin or an agonist thereof, wherein the exendin is exendin-3 or exendin-4, and the exendin agonists include exendin-4 (1-30), exendin-4 (1-30) amide, exendin-4 (1-28) amide, <sup>14</sup>Leu, <sup>25</sup>Phe exendin-4 amide, and <sup>14</sup>Leu,

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<sup>25</sup>Phe exendin-4 (1-28) amide (page 10, line 19 to page 11, line 11). Further, Beeley teaches that the method is useful for, among others, reducing the cardiac risk (abstract, and page 10, lines 16-19). Furthermore, Beeley teaches that the method is also useful for reducing appetite (food intake), reducing the weight of subjects, and lowering plasma lipid levels (abstract, page 1, lines 18-24, and page 10, lines 6-15), which comprise cholesterol and triglycerides (as evidenced by Beers et al., the Merck Manual, 1999, 17<sup>th</sup> edition, page 200, the last paragraph of the left column). Furthermore, Beeley teaches that the exendin or the exendin agonist is administered preferably by injection, that the dose for the administration can be about 10-30 ug to about 1 mg, or about 30 ug to about 500 ug per day (page 9, line 28 to page 10, line 3).

Therefore, with respect to claims 1, 3, 5, 6, 9-14, 24, 26, 28, 29, 32-36 and 41, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to identify and to treat a subject having elevated postprandial triglyceride levels by administering an exendin or an agonist thereof following the method taught by Beeley in order to reduce the cardiac risk, as Karpe indicates that the postprandial elevation of plasma triglycerides is more closely linked to the risk of CHD. The person of ordinary skill in the art would have been motivated to do so in order to treat and reduce the risk of CHD, and reasonably would have expected success because Beeley has taught that exedin can reduce the cardiac risk, and that exedin can lower plasma lipids, and control obesity (by reduce food intake), which are well known and important risk factors for in cardiovascular diseases. While such a treatment is implemented to a subject identified as one at the cardiac risk because of elevated postprandial triglyceride levels, it would be inherent that said subject's postprandial plasma triglyceride levels

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would be lowered, as the active ingredient, method steps and patient population would be the same as that of the present invention.

With respect to claims 2, 4, 7, 8, 25, 27, 30 and 31, although Beeley does not specify the continuous administration (as claims 2 and 25) or a subcutaneous injection (as claims 4 and 27), nor a dose range of about 1-30 ug to about 100 ug, or about 3 ug to about 50 ug per day (as claims 7, 8, 30 and 31), however, given the state of the prior art, determination of an appropriate way of administering a drug, and its applicable dose range is well within the purview of a person of ordinary skill in the art, and therefore, "administered continuously", "a subcutaneous injection", and said dose ranges are considered *prima facie* obvious in the absence of any unexpected result. Mere determination of optimal dosage, and route and duration of administration of treatment regimens does not constitute novel inventive concept.

Claims 15 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Karpe et al. (Metabolism, 1999, 48:301-307), and Beeley et al. (WO 98/30231), as applied to claims 1-14, 24-36 and 41 above, and further in view of Wagle et al., US 6,326,396 B1.

The teachings of Karpe and Beeley are reviewed above. Neither reference teaches to use an exendin or an exendin agonist in combination with a statin for lowering triglyceride levels.

Wagle teaches that HMG-CoA reductase inhibitors (also known as "statins") are agents acting directly on plasma triglyceride and cholesterol content, and are effective in lowering triglyceride and cholesterol content, and that lowering of circulating lipids has been to reduce the cardiovascular morbidity (column 2, lines 28-33).

It would have been *prima facie* obvious to one of ordinary skill in the art to combine the teachings of the references and to combine an exendin or an exendin agonist with a statin (HMG-

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CoA reductase inhibitor) for lowering plasma lipid levels because each of the two drugs is well known for its effect on lowering plasma lipid. The instant situation is amenable to the type of analysis set forth in *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant method claims, given the teaching of the prior art of methods using exendins or exendin agonists, or statins for lowering plasma lipids or treating diabetes; it would have been obvious to combine the two drugs for lowering plasma triglyceride and cholesterol because the idea of doing so would have logically followed from their having been individually taught in the prior art to be useful for the same purpose of lowering plasma lipid. Thus, claims that require no more than adding together of two conventional drugs set forth *prima facie* obvious subject matter. The person of ordinary skill in the art would have been motivated to do so because Wagle teaches that lowering plasma triglyceride and cholesterol is beneficial for reducing the cardiovascular morbidity, and reasonably would have expected success because both drugs had been demonstrated in the prior art to be effective on lowering plasma lipid.

#### **(10) Response to Argument**

##### ***I. Prior art rejection of claims 1-14, 24-36 and 41 under 35 U.S.C. 103(a)***

The central issue is whether it is obvious to combine the teachings of the two prior art references, and whether the combined the teachings made the present invention obvious.

At pages 3-4 of the Brief, Appellant argues that the Office has failed to establish that one of ordinary skill in the art would have found it obvious to combine the teachings of Karpe and Beeley, which teach that postprandial elevation of plasma triglycerides is more closely linked to coronary heart disease (CHD) than the fasting level (by Karpe), and that the use of exendins and exendin agonists to inhibit food intake (by Beeley); that, *according to the Office*, Beeley also discloses the use of exendins and exendin agonists to reduce plasma lipid levels and cardiac risk, however, the Beeley reference contains no teaching regarding the use of exendins to lower triglycerides, and does not mention triglycerides at all; and that it is known in the art that the lowering of lipids in general does not predict change in a particular lipid component, one of ordinary skill in the art would neither have expected exendins and exendin agonists to lower plasma triglyceride levels, nor have found it obvious to combine Beeley's exendins and exendin agonists with Karpe's subjects having elevated triglyceride levels.

Appellant's argument has been fully considered, but is not deemed to be persuasive for the following reasons. While Beeley teaches the use of exendins and exendin agonists to inhibit food intake (as pointed by applicants), more importantly, Beeley also teaches (not "according to the Office") the use of exendins and exendin agonists for *reducing the cardiac risk* (and lowering plasma lipid levels), based on which the present rejection is made. Note, MPEP states "a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft*

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Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989)” (MPEP 2123 [R-5], I.).

In response to Appellant’s argument that it is not obvious to combine the references, the examiner recognizes that obviousness can be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Karpe teaches a method of identifying subjects at the risk of developing coronary heart disease (CHD) by measuring the postprandial (after a meal) plasma triglyceride levels, wherein the triglyceride levels are elevated; and Beeley teaches the use of exendins for reducing the cardiac risk. Therefore, it is instantly obvious for a person having ordinary skill in the art to treat the subjects at the risk of developing CHD (identified by Karpe’s method of detection) with an exendin in order to reduce cardiac risk in these subjects (Beeley’s method of treatment). Karpe’s patients at the risk of developing CHD are certainly “subjects in need of” treatment for reducing the cardiac risk, such as by the method taught by Beeley. Therefore, it is obvious to combine the teachings of the Karpe and Beeley references. As Karpe’s method of identification and the subjects identified (at the risk of developing CHD), and Beeley’s method of treatment and active ingredient for the treatment *are the same* as the patient population, method steps and active ingredient of the present invention, the treatment of Karpe’s patients with Beeley’s exendin would inherently lower triglyceride levels in these subjects even though Beeley does not

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specifically mention exendin for lowering triglyceride levels. Therefore, the present invention is obvious and unpatentable over the cited prior art references.

Appellant further argues, on page 4 of the Brief, that Beeley does not disclose lowering plasma triglyceride levels or identifying subjects with elevated triglyceride levels; that the Office appears to argue that subjects at cardiac risk inherently possess elevated triglyceride levels; and that *obviousness* cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. See *In re Rijckaert*, 9 F.2d 1531 (Fed. Cir. 1993), hence, the Office improperly relied upon the alleged *inherency* of claim limitations in its construction the rejection under §103.

Appellant's argument has been fully considered, but is not deemed to be persuasive because obviousness and inherency are not the same concept. In the instant case, obviousness is not predicated on the teachings of Appellant, rather, it is based on the combined teachings of the prior art (see discussion above). With respect to inherency, it is established based on the fact that the patient population, method steps and active ingredient of the present invention and the combined teachings of the prior art references are the same, even though Beeley does not expressly make it clear that exendin would lower triglyceride levels (Beeley teaches that exendin would lower plasma lipid, which comprise cholesterol and triglycerides, as evidenced by Beers). MPEP states "[T]here is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference" (MPEP 2112 [R-3], II.). With respect to Appellant's argument that Beeley does not disclose identifying subjects with elevated triglyceride levels, which is taught by Karpe, it is against the references individually. One cannot show

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nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986) (see MPEP 2145 [R-3], IV.). In the instant case, it is the combined teachings of Karpe and Beeley, which render the present invention obvious for the reasons above. Further, contrary to Appellant's argument, the Office did not argue that subjects at cardiac risk inherently possess elevated triglyceride levels, rather, it is that Karpe teaches subjects with elevated postprandial triglyceride levels are at cardiac risk. Once again, the inherency in the instant case is based on the fact that the patient population, method steps and active ingredient of the present invention are the same as that of the combined teachings of the prior art references.

At pages 4-5 of the Brief, Appellant argues that even assuming, *arguendo*, that the Office's reliance upon the alleged inherency of claim limitations is proper, the ground of rejection flounders on the Office's failure to establish inherency; that inherency requires a certainty that a property or characteristic exists, and "[I]nherency, however, may not be established by probabilities or possibilities" (*Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991)); that the Office fails to show that methods of inhibiting food intake as taught by Beeley necessarily lower plasma triglyceride levels; and that in fact, evidence suggests that reducing food intake does not necessarily result in lowering triglyceride levels. Appellant further argues that in an effort to identify a link between reducing food intake and lowering triglyceride levels, the Office cites Beeley's remarks on the uses of exendins or exendin agonists in reducing plasma lipid levels and cardiac risk (see Office Action mailed on 12/14/06, page 4, lines 9-12), however, the Office has failed to show that a reduction of plasma lipid levels

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generally or cardiac risk necessarily results in the lowering of triglyceride levels specifically as is required to support a rejection based on inherency.

Appellant's argument has been fully considered, but is not deemed to be persuasive because, as addressed above, inherency in the instant case is not established by probabilities or possibilities, rather, it is established by a certainty, i.e., based on the fact that the patient population, method steps and active ingredient of the present invention are the same as that of the combined teachings of the prior art references, and thus, the prior art method would inherently lower triglyceride levels even though the prior art does not expressly disclose such. Further, Appellant has wrongly interpreted the Office Action, as there is no effort by the Examiner to try to identify a link between reducing food intake and lowering triglyceride levels. Contrary to Appellant's argument, there is no mentioning of reducing food intake on page 4 of the Office Action. Reducing food intake has never been a central issue in the rejection of any of the Office Actions, and it does not form the basis for the rejection. Once again, the rejection is based on, with respect to the Beeley reference, the teachings of the use of extendins and extendin agonists for *reducing the cardiac risk*.

At page 5 of the Brief, Appellant argues that triglycerides represent one of several classes of plasma lipids, others include HDL and LDL, and these classes of plasma lipids are differentially regulated; that, as a result, a number of therapeutic agents affect one class of plasma lipids without affecting another (citing multiple references); and that in this regard, not all subjects administered extendins show a decrease in triglycerides, only those in need of such treatment.

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Appellant's argument has been fully considered, but is not deemed to be persuasive for the following reasons. By definition, plasma lipid includes two major components, cholesterol and triglycerides (as evidenced by Beers et al., the Merck Manual, 1999, 17<sup>th</sup> edition, page 200, the last paragraph of the left column), and HDL and LDL are subclasses of cholesterol. While the Examiner acknowledges that plasma lipids are differentially regulated, and therapeutic agents affecting one class of plasma lipids may not necessarily affect another, this argument is irrelevant because the rejection is NOT based on that Beeley teaches that exendin can lower plasma lipid levels, and therefore, triglyceride levels would be inherently lowered since triglyceride is a part of plasma lipid. Rather, the rejection is based on the combined teachings of the prior art, and the inherency is based on the fact that the patient population, method steps and active ingredient of the present invention are the same as that of the combined teachings of the prior art references.

At page 6 of the Brief, Appellant argues that the Office's use of inherency in the obviousness rejection is based on hindsight, and the Office has used the knowledge from appellants' disclosure that an exendin or an exendin agonist lowers plasma triglyceride levels as a roadmap to combine Beeley's exendins with Karpe's subjects having elevated triglyceride levels; that the Office has failed to show that one of ordinary skill in the art would have had a reasonable expectation that reducing plasma lipid levels or cardiac risk would result from administering exendins or exendin agonists; and that the Office has not provided objective evidence or reasoning to support that one of ordinary skill in the art would have correlated the reduction of plasma lipid levels or cardiac risk with the lowering of triglyceride levels despite

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published evidence that decreases in lipids are not necessarily correlated with decreases in triglycerides.

Appellant's argument has been fully considered, but is not deemed to be persuasive for the following reasons. In response to applicant's argument that the examiner's conclusion of obviousness and inherency is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, the rejection is entirely based on the knowledge established in the prior art (as discussed above). Further, it is unclear with respect to the argument that the Office has failed to show that one of ordinary skill in the art would have had a reasonable expectation that reducing plasma lipid levels or cardiac risk would result from administering exendins or exendin agonists, because it is irrelevant since Beeley expressly teaches that exendin is useful for reducing the cardiac risk and for lowering plasma lipid levels. With respect to the argument that the Office has not provided objective evidence or reasoning to support that one of ordinary skill in the art would have correlated the reduction of plasma lipid levels or cardiac risk with the lowering of triglyceride levels, the rejection clearly provides such evidence or reasoning. The evidence is provided by the combined teachings of Karpe and Beeley, as reviewed above, and the reasoning (or logic) is, once again, that Karpe teaches subjects with elevated postprandial triglyceride levels are at cardiac risk, thus, obviously these subjects need treatment for reducing such a risk. Since Beeley

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expressly discloses that exendin is useful for reducing the cardiac risk, it becomes instantly clear to one of ordinary skill in the art that it would be beneficial or therapeutic to treat the subjects with elevated postprandial triglyceride levels (identified by Karpe's method) with Beeley's exendins or exendin agonists. Such an obvious method of treatment comprises the same method steps, same active ingredient and the same patient population, and therefore, leads to inherency that triglyceride levels in these subjects are lowered, as a result of the same treatment in the same patients.

Appellant further argues, on page 6 of the Brief, that "[T]o have a reasonable expectation of success, one must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *Medichem, S.A.v. Rotabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006); and that in light of the vast number of treatments for inhibiting food intake and for reducing plasma lipid levels and cardiac risk, combined with the lack of predictability that such treatments would result in lowering triglyceride levels, one of ordinary skill in the art would neither have found it obvious to combine Beeley's methods of administering exendins and exendin agonists with Karpe's subjects at cardiac risk, nor have reasonably expected that such methods would result in lowering triglyceride levels in the subjects.

Appellant's argument has been fully considered, but is not deemed to be persuasive because the combined teachings of the prior art clearly indicate that the subjects with elevated postprandial triglyceride levels are at cardiac risk, and are certainly in need of treatment for reducing such a risk, and that exendin is useful for reducing such a risk. The fact that there are

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vast numbers of treatments for inhibiting food intake and for reducing plasma lipid levels and cardiac risk does not constitute any reason for avoiding the use of exendin for reducing cardiac risk. At a minimum, it would be one of the available treatments for reducing cardiac risk.

Additionally, as Beeley teaches that exendin can also lower plasma lipids, and control obesity (by reducing food intake), which are well established and important risk factors in cardiovascular diseases, it provides stronger reasons to use exendin for reducing cardiac risk because it is capable of reducing multiple risk factors. Therefore, one of ordinary skill in the art would have found it obvious to combine Beeley's methods of administering exendins and exendin agonists with Karpe's subjects at cardiac risk, and such methods would inherently result in lowering triglyceride levels in the subjects.

## ***II. Prior art rejection of claims 15 and 37 under 35 U.S.C. 103(a)***

The central issue is whether it is obvious to combine the teachings of the Karpe and Beeley references, and whether the combination with the third reference by Wagle made the presently claimed invention obvious.

At pages 6-7 of the Brief, Appellant argues that for at least the reasons above, Karpe and Beeley in view of Wagle do not teach or suggest identifying a subject with elevated postprandial triglyceride levels and treating such subjects with exendins or exendin agonists, as the compounds disclosed in Wagle are small molecules while the claims that are the subject of the present appeal are all directed to a particular group of peptides, and whatever else Wagle discloses, it too does nothing to remedy the deficiencies of Karpe and Beeley; and that the Office has provided no evidence or reasoning why one skilled in the art would combine these

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references, especially when they address such divergent molecules to arrive at the presently claimed invention.

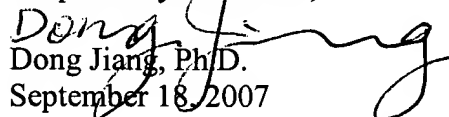
Appellant's argument has been fully considered, but is not deemed to be persuasive for the reasons addressed above. Further, the reason as to why one skilled in the art would combine these references, especially when they address such divergent molecules to arrive at the presently claimed invention is because the present claims 15 and 37 recite the limitation requiring an addition of another divergent molecule, a statin. Wagle teaches such a group of such molecules, HMG-CoA reductase inhibitors (also known as "statins"), which act directly on plasma lipid content (triglyceride and cholesterol), are effective in lowering triglyceride and cholesterol content, and reduce the cardiovascular morbidity. Therefore, the combined teachings of the cited prior art references render the present invention obvious and not novel.

For the above reasons, it is believed that the rejections should be sustained.

**(11) Related Proceeding(s) Appendix**

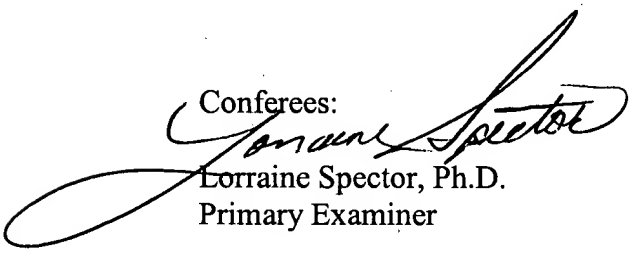
No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

Respectfully submitted,

  
Dong Jiang, Ph.D.  
September 18, 2007

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